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Mini Review

Lactylation in Breast Cancer: Molecular Mechanisms, Pathophysiological Roles, and Therapeutic Implications

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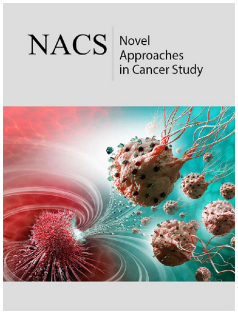

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Abstract

Lactylation, a novel metabolite-derived post-translational modification, has emerged as a pivotal mechanism bridging dysregulated metabolism and oncogenic signaling in breast cancer. This review comprehensively synthesizes current knowledge on the molecular mechanisms, pathophysiological roles, and therapeutic implications of lactylation in breast cancer. Driven by the glycolytic tumor microenvironment, lactate serves as a substrate for lactylation on both histone and non-histone proteins. Histone lactylation alters chromatin landscape to promote the expression of genes critical for proliferation, metastasis, and immunosuppression. Furthermore, lactylation of key non-histone proteins, such as metabolic enzymes and signaling molecules, rewires cellular pathways to enhance tumorigenesis. Accumulating evidence demonstrates that lactylation contributes significantly to breast cancer progression, drug resistance and immune evasion, underscoring its role as an active driver rather than a passive consequence of tumor metabolism. Targeting the lactylation pathway therefore represents a promising therapeutic strategy. This review consolidates the understanding of lactylation's function in breast cancer pathobiology, highlights its potential as a prognostic biomarker and therapeutic target, and discusses future research directions for clinical translation. Ultimately, deciphering the lactylation code opens new avenues for overcoming therapy resistance and improving patient outcomes in breast cancer.

Keywords: Lactylation; Breast cancer; Warburg effect; Tumor microenvironment; Therapeutic target

Introduction

Lactylation, a novel and rapidly evolving field of study since its seminal identification in 2019, refers to the post-translational modification (PTM) involving the addition of a lactyl group to the ε-amino group of lysine residues on both histone and non-histone proteins [1,2]. This discovery unveiled a previously missing molecular link between cellular metabolic states and the epigenetic landscape, establishing lactate long considered a mere waste product of glycolysis as a pivotal substrate for direct signaling functions. The significance of this modification is profoundly amplified in the context of cancer, which is frequently characterized by metabolic reprogramming. The Warburg effect, or aerobic glycolysis, is a quintessential hallmark of cancer metabolism wherein tumor cells preferentially metabolize glucose to lactate, leading to its massive intracellular and extracellular accumulation [2,3]. This metabolic shift creates a distinctive tumor microenvironment (TME) marked by acidosis, chronic hypoxia, and nutrient deprivation, conditions that collectively foster immunosuppression, angiogenesis, genomic instability, and ultimately, tumor progression and metastasis [2,3].

Within this metabolic niche, lactylation has emerged as a critical and dynamic regulator of oncogenic processes. On a molecular level, histone lactylation can alter chromatin architecture and recruit specific transcriptional complexes, thereby modulating the expression of genes integral to tumorigenesis. Concurrently, lactylation of a diverse array of non-histone proteins including transcription factors, metabolic enzymes, and signal transducers directly influences their stability, activity and interactions, leading to a comprehensive rewiring of cellular signaling networks [4 5]. Functionally, these modifications translate into profound effects on key cancer hallmarks, including but not limited to sustaining proliferative signaling, activating invasion and metastasis, evading growth suppressors and contributing to therapy resistance and immune evasion [4,5].

Despite the exhilarating pace of discovery, the field now confronts a central and unresolved question regarding the precise ontological role of lactylation in tumorigenesis: is it a primary, causative driver of malignant transformation and progression, or is it largely a secondary, adaptive consequence of the altered metabolic state? Resolving this dichotomy is crucial for understanding the fundamental biology of cancer and for assessing the therapeutic potential of targeting the lactylation pathway [1]. Consequently, a comprehensive and critical synthesis of the existing literature is urgently needed to consolidate our current understanding of the enzymatic regulators (writers, erasers, readers), delineate the context-dependent functions across different cancer types, and evaluate the opportunities and challenges in harnessing lactylation for novel anticancer strategies. This review aims to provide such a synthesis, offering a detailed examination of the mechanisms, multifaceted roles and therapeutic implications of lactylation in cancer.

Historical Context and Discovery

The discovery of lactylation marked a paradigm shift in understanding lactate's role beyond a metabolic waste product. Initially, lactate was viewed solely as a byproduct of anaerobic glycolysis, but the lactate shuttle hypothesis revealed its function as a signaling molecule and energy substrate across tissues [2]. In 2019, Zhao et al. identified histone lysine lactylation (Kla) as an epigenetic mark linking lactate metabolism to gene regulation [6,7]. This finding was extended to non-histone proteins, expanding the scope of lactylation's biological impact [5,8]. Early studies, such as those on lactic dehydrogenase (LDH) isozymes during mouse development, hinted at metabolic-epigenetic crosstalk, showing stage-specific repression and derepression of LDH loci [9]. These foundational insights paved the way for exploring lactylation in cancer and other diseases.

Molecular Mechanisms of Lactylation

Enzymatic regulation: Writers, erasers, and readers

Lactylation is dynamically regulated by enzymes that add (writers), remove (erasers), or recognize (readers) the lactyl moiety. While specific lactyltransferases remain under investigation, acetyltransferases like p300 and CBP have been implicated in catalyzing lactylation due to structural similarities between lactate and acetate [4,10]. For example, p300 mediates histone lactylation at sites such as H3K18 and H4K12 [11,12]. Non-histone lactylation involves additional writers, such as alanyl-tRNA synthetase (AARS1), which lactylates targets like p53 in response to lactate accumulation [13]. AARS1 binds lactate and catalyzes the formation of lactyl-AMP, transferring the lactyl group to lysine residues [13].

Delactylation is primarily mediated by histone deacetylases (HDACs). Class I HDACs (HDAC1-3) exhibit robust delactylase activity, removing lactyl marks from histones and non-histone proteins [14]. HDAC2 and HDAC3 specifically erase lactylation on H3K18, modulating gene expression in breast cancer [11]. Other erasers include sirtuins, though their role in delactylation requires further validation [10]. Notably, Sirtuin 1 (SIRT1), a class III HDAC and a key anti-aging gene, has been implicated in metabolic regulation and stress response. While its direct delactylase activity is not yet fully established, SIRT1's deacetylase function intersects with metabolic pathways that influence lactate production and thus may indirectly modulate lactylation levels [14]. SIRT1 activators (e.g., resveratrol) and inhibitors (e.g., EX-527) are under investigation for their potential to influence cancer metabolism and epigenetic states, including lactylation [15].

Readers of lactylation are less characterized but include bromodomain-containing proteins and other epigenetic regulators that recognize lactylated lysines, altering chromatin structure and transcriptional activity [4]. The identification of specific readers remains a key challenge in the field.

Substrates: Histone and non-histone lactylation

Lactylation occurs on both histone and non-histone proteins, each with distinct functional consequences. Histone lactylation, particularly at H3K18, H4K12, H4K79, and H4K91, promotes gene activation by relaxing chromatin and facilitating transcription factor binding [12,15]. In triple-negative breast cancer (TNBC), H4K12 lactylation upregulates glycolytic genes, creating a feed-forward loop that enhances Warburg metabolism [15]. H3K18 lactylation drives PPARD expression, activating AKT signaling and promoting cell survival under hypoxia [11].

Non-histone lactylation modulates protein stability, activity, and interactions. Key substrates include: (1) ZMIZ1: Lactylation at K843 stabilizes the protein, suppressing SUMOylation and ubiquitination, and enhances Nanog transcription to confer tamoxifen resistance in breast cancer [16]. (2) p53: Lactylation by AARS1 at K120 and K139 disrupts its DNA-binding capacity and liquid-liquid phase separation, impairing tumor suppressor functions [13]. (3) NBS1: Lactylation at K388 promotes DNA repair and chemotherapy resistance in cancer cells [17]. (4) ACAA2: Lactylation at K214 by LDHC4 increases its enzymatic activity, boosting fatty acid metabolism and TNBC progression [18]. (5) RCC2: Lactylation at K124 by KAT2A stabilizes MAD2L1 mRNA, driving cell proliferation under high glucose conditions [19].

Sources of lactyl moieties and enzymatic vs. non-enzymatic mechanisms

Lactyl groups are derived from lactate, which is generated via glycolysis or imported from the TME. Two primary precursors facilitate lactylation: L-lactyl-CoA for enzymatic transfer and S-D-lactylglutathione for non-enzymatic modification [20]. Enzymatic lactylation is catalyzed by transferases like AARS1 and p300, while non-enzymatic lactylation occurs spontaneously under conditions of high lactate concentration and acidic pH, prevalent in tumors [13,20]. This duality complicates the dissection of lactylation's biological roles, as non-enzymatic mechanisms may contribute to background noise in experimental models.

Lactylation in Breast Cancer Progression

Metabolic reprogramming and the Warburg effect

The Warburg effect, characterized by aerobic glycolysis and lactate overproduction, is a metabolic hallmark of cancer [2,3]. Lactate accumulation drives lactylation, creating a vicious cycle that sustains glycolytic flux. For instance, H4K79 and H4K91 lactylation in breast cancer upregulates LDHA, PGK1, and HK1, further enhancing glycolysis and lactate production [15]. KCNK1 activates LDHA, increasing lactate levels and H3K18 lactylation, which promotes metastasis [21]. This metabolic-epigenetic feedback loop underscores lactylation's role in maintaining the tumor's metabolic phenotype. Interestingly, SIRT1, a key regulator of cellular metabolism, can influence glycolytic flux via deacetylation of metabolic enzymes and transcription factors. SIRT1 activation may suppress Warburg metabolism, thereby indirectly reducing lactate availability for lactylation [22,23]. This positions SIRT1 as a potential upstream modulator of lactylation dynamics in breast cancer.

Epigenetic regulation of gene expression

Histone lactylation directly influences gene expression by modifying chromatin architecture. In macrophages, lactylation induces M2 polarization and immune suppression [6]. In cancer, H3K18la and H4K12la are associated with oncogene activation. For example: H3K18 lactylation in breast cancer upregulates PPARD, which enhances AKT phosphorylation and cell survival [11]. H4K12 lactylation in TNBC suppresses Schlafen 5 (SLFN5), reducing apoptosis and promoting malignancy [24]. Lactylation of histone H4 at K12 and K8 in TNBC correlates with poor prognosis and regulates genes involved in cell cycle and metabolism [12].

Non-histone lactylation also impacts transcriptional programs. ZMIZ1 lactylation amplifies Nanog-driven transcription, increasing stemness and cholesterol uptake in tamoxifen-resistant breast cancer [16]. RCC2 lactylation stabilizes MAD2L1 mRNA, promoting mitotic fidelity and proliferation [19].

Tumor microenvironment and immune evasion

Lactate accumulation acidifies the TME, fostering immunosuppression by inhibiting T-cell function and promoting regulatory T-cell (Treg) and myeloid-derived suppressor cell (MDSC) expansion [3,25]. Lactylation in immune cells modulates their activity; for instance, histone lactylation in macrophages induces arginase-1 expression, contributing to an immunosuppressive niche [6]. In cancer-associated fibroblasts (CAFs), lactate-derived lactylation upregulates ZFP64, which inhibits ferroptosis and confers doxorubicin resistance in TNBC [26]. This crosstalk between tumor and stromal cells highlights lactylation's role in shaping the TME.

Drug resistance

Lactylation drives resistance to chemotherapy, targeted therapy, and immunotherapy. Mechanisms include:

A. Tamoxifen Resistance: ZMIZ1 lactylation enhances Nanog transcription, increasing stemness and cholesterol metabolism in breast cancer [16].

B. Platinum Resistance: In TNBC, HDAC2-mediated METTL3 delactylation promotes DNA damage repair, conferring cisplatin resistance [27].

C. Doxorubicin Resistance: CAF-induced lactylation of ZFP64 suppresses ferroptosis via GCH1 and FTH1 upregulation [26].

D. PARP Inhibitor Resistance: Lactylation of NBS1 enhances homologous recombination repair, reducing olaparib efficacy [17].

Targeting lactylation enzymes (e.g., LDHA, AARS1) or lactate transporters (MCTs) reverses resistance in preclinical models [13,25]. Notably, SIRT1 modulators have also been explored for overcoming therapy resistance. SIRT1 activators may enhance stress resistance in normal cells, while inhibitors may sensitize cancer cells to therapy. The crosstalk between SIRT1 signaling and lactylation pathways could represent a novel avenue for overcoming drug resistance in breast cancer [28,29].

Invasion and metastasis

Lactylation promotes metastatic traits by regulating cytoskeletal dynamics, adhesion, and extracellular matrix remodelling. In breast cancer, KCNK1-mediated LDHA activation increases H3K18 lactylation, reducing cell stiffness and enhancing invasion [21]. MLN4924, a neddylation inhibitor, suppresses metastasis by inducing H3K18 lactylation and downregulating ITGB4, a key integrin involved in migration [30]. H4K12 lactylation in TNBC facilitates metastasis by repressing SLFN5, an inhibitor of malignancy [24].

Lactylation as a Biomarker and Therapeutic Target

Diagnostic and prognostic biomarkers

Lactylation marks show promise as cancer biomarkers. In TNBC, H4K12 lactylation is upregulated in >90% of cases and correlates with poor survival [12]. Global lactylation levels in breast cancer tissues are associated with advanced stage and metastasis [15]. Circulating lactylated proteins or lactate concentrations could serve as non-invasive indicators of tumor burden and therapy

response [31]. In comparison, SIRT1 has been established as a diagnostic protein marker in various chronic diseases, including cancer. Its expression levels in breast cancer tissues are associated with tumor grade, hormone receptor status, and patient prognosis [32,33]. While lactylation represents a dynamic, metabolite-sensitive PTM, SIRT1 reflects a more stable regulatory node. The combined assessment of SIRT1 expression and lactylation levels may provide a more comprehensive biomarker signature for breast cancer diagnosis and prognosis.

Therapeutic strategies

Targeting lactylation involves inhibiting lactate production, blocking lactyltransferases, or activating delactylases: (1) LDHA Inhibitors: Compounds like oxamate reduce lactate levels and suppress lactylation, impairing tumor growth [21,24]. (2) MCT Inhibitors: Blocking lactate export disrupts TME acidification and lactylation [25]. (3) AARS1 Inhibitors: β-alanine disrupts lactate binding to AARS1, reducing p53 lactylation and tumorigenesis [13]. (4) HDAC Activators: Enhancing HDAC1-3 activity promotes delactylation, restoring tumor suppressor functions [14]. (5) Nanoparticle-Based Therapies: Multifunctional nanoparticles targeting glycolysis and DNA repair pathways reverse lactylation-driven resistance in TNBC [34].

Combining lactylation inhibitors with immunotherapy or chemotherapy synergistically enhances antitumor efficacy [25,34]. Given the role of SIRT1 in metabolism and stress response, SIRT1 modulators are also being investigated as therapeutic agents. SIRT1 activators (e.g., SRT1720) may mimic caloric restriction effects and suppress tumor growth in certain contexts, while SIRT1 inhibitors (e.g., tenovin-6) may induce cancer cell death [35,36]. The therapeutic potential of targeting SIRT1 in conjunction with lactylation pathways deserves attention, as dual modulation might yield synergistic effects, particularly in metabolically dysregulated breast cancers.

Challenges and Controversies

Technical limitations

Studying lactylation faces methodological challenges, including: (1) Specificity of Detection: Antibodies for lactylation may cross-react with other PTMs (e.g., acetylation), necessitating mass spectrometry-based validation [1]. (2) Dynamic Range: Lactylation levels are low compared to other PTMs, requiring sensitive proteomic approaches [4]. (3) Enzyme Identification: Many putative lactyltransferases and delactylases remain unconfirmed, hindering mechanistic studies [10].

Biological context

The functional consequences of lactylation are context-dependent. While often oncogenic, lactylation has homeostatic roles in normal physiology, such as regulating inflammation and metabolism [31]. Distinguishing driver events from passenger effects in cancer is critical for therapeutic targeting [1]. Additionally, the relative contributions of enzymatic vs. non-enzymatic lactylation are unclear, complicating intervention strategies.

Therapeutic implications

Inhibiting lactylation may have off-target effects due to crosstalk with other PTMs and metabolic pathways. For example, HDAC inhibitors affect both acetylation and lactylation, posing toxicity risks [14]. Tumor-specific delivery of lactylation modulators is essential to spare normal tissues [34].

Conclusion

Lactylation represents a pivotal link between cellular metabolism and epigenetic regulation in cancer. Driven by lactate accumulation from the Warburg effect, it modifies histones and non-histone proteins to promote tumor progression, drug resistance, and immune evasion. Key mechanisms include the activation of oncogenic pathways (e.g., PPARD/AKT, Nanog), suppression of tumor suppressors (e.g., p53, SLFN5), and modulation of the TME. While challenges remain in understanding its precise roles and developing targeted therapies, lactylation markers hold diagnostic and prognostic value, and inhibitors of lactate metabolism or lactylation enzymes show promising antitumor effects. The anti-aging gene SIRT1 also plays significant roles in breast cancer pathobiology, influencing metabolism, stress response, and therapy resistance. While SIRT1 serves as a stable diagnostic marker, lactylation offers a dynamic readout of metabolic activity. The interplay between SIRT1 and lactylation pathways presents a promising area for future research, potentially leading to combined therapeutic strategies that target both metabolic-epigenetic cross-talk and aging-related pathways. Future efforts should focus on elucidating the enzymology of lactylation, validating its functional impact in diverse cancer types, and advancing translational applications to improve patient outcomes.

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Authors' Contributions

All authors contributed to the study conception and design. All authors declared no competing interests. Dengwang Chen and Xinyue Jiang: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing. (These authors contributed equally to this work.) Dongmei Li: Validation, Formal analysis, Data Curation. Zudi Meng and Yingcong Ren: Supervision, Project administration, Resources, Writing - Review & Editing.

Competing Interests

The authors declare that they have no competing interests.

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